disclosure a description of the invention defined by the claims. MPEP §2163 I A. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. MPEP §2163. The rejected claims all relate to well known methods of protein immobilization and modifications of proteins to allow convenient purification and tracking of the proteins. As one skilled in the art often practice these techniques and are thus familiar with them, the disclosure of the present application provides sufficient detail for an artisan to reasonably conclude that the inventor had possession of the claimed invention. On the other hand, the Examiner has not stated any reason why an artisan could not determine what the invention is based on the disclosure. The written rejections to claims 22-27 should therefore be properly withdrawn.

2. Enablement Rejection to Claim 22

A patent need not teach, and preferably omits, what is well known in the art. MPEP §2164.01. There are a wide variety of techniques that have been well established and routinely used by those skilled in the pertinent art to immobilize polypeptides. Some of these techniques became known nearly two decades ago, whereas new methods continue to emerge to this date. These techniques achieve immobilization of proteins by various means, such as by direct linkage via a covalent or non-covalent bond between the protein and the solid support, or by a linker that provides various functional groups to allow the attachment of a protein to a solid support. Direct linkage by a covalent bond may be effectuated by chemical reactions between the functional groups on the protein and the solid support. Some examples of such functional groups include amine, carboxylic acid, and sulfhydryl groups. Direct linkage by a non-covalent bond often relies on the interaction between a tag and a tag binder, which are present separately on the protein and the solid support. Some examples of tag and tag binder pairs are: biotin and avidin/streptavidin/neutravidin; cell receptor-ligand pairs such as transferrin, c-kit, cytokine, chemokine, interleukins and their receptors; and cadherein

family, integrin family, selectin family, and their respective ligands. More suitable binding pairs can be found in literature, *e.g.*, Pigott & Power, *The Adhesion Molecule Facts Book I* (1993). When there are no appropriate functional groups to allow direct linkage between a protein and a solid support, a variety of linkers can be used, such as those available from Pierce Chemical Company, Rockford, Illinois.

A wide array of solid support are well known to and frequently used by those skilled in the art. Many solid support have proven in past use to have no significant effect on the biological activities of immobilized proteins. Thus, one skilled in the art has ample selections of solid support should a particular choice be unfit for the purpose of practicing the invention.

There is a vast body of knowledge on different types of linkers and solid support, as well as the methods of using them to immobilize proteins. Some examples of the large body of scientific literature and US Patents on polypeptide immobilization are: Jonsson et al., *Biochem. J.* 227: 363-371; 373-378. 1985; Kobatake et al., *J. Biotechnol.* 38: 263-268. 1995; O'Shannessy et al., *Anal. Biochem.* 229: 119-124. 1995; Turkova J., *J. Chromatogr. B. Biomed. Sci. Appl.* 722: 11-31. 1999; US Patent Nos. 4,246,350; 4582,622; 4,757,014; 4,808,530; 4,952,519; 5,405,766; 5,922,531; 6,180,378.

In summary, the methodologies of protein immobilization are routinely used and one of ordinary skill is familiar with them. There is no need to rely on the teaching of the instant application to practice this aspect of the invention. The Examiner has not offered any reason as to why one skilled in the art would not be able to practice the invention as claimed. The enablement rejection to claim 22 should be properly withdrawn.

3. Enablement Rejections to Claims 23-27

As far as the use of epitope tags, fusion protein sequences, and enzyme cleavable linkers is concerned, Applicants do not agree with the Examiner's assertion that there is no teaching in the application. In fact, the specification provides detailed information in this regard. For example, the attachment of a poly His tag at either

terminus of a recombinant polypeptide is discussed on page 15 lines 22-23; the fusion of an additional sequence to facilitate the production and isolation of a recombinant polypeptide is taught on page 15 lines 23-32; the use of enzyme cleavable linkers is disclosed on page 16 lines 1-14.

More importantly, various techniques using epitope tags, enzyme cleavable linkers, or thioredoxin sequence to aid the isolation of recombinant polypeptides are also well developed and routinely practiced by those skilled in the art. To prove the point, Applicants call the Examiner's attention to the large number of commercially available cloning/expression vectors that contain various of epitope tags, linkers, or a thioredoxin sequence. As a few examples, the enclosed copies of product information sheets and technical brochures from several companies describe a variety of epitope tags (such as 6-His), which are frequently used to facilitate purification and/or tracking of recombinant polypeptides. It is well known to those skilled in the art that a small epitope of 3-14 amino acids will rarely affect the biological functions of the tagged protein (see Exhibit A, Boehringer-Mannheim product information manual, page 1.4), and that such epitope can be attached at either the N-terminal or C-terminal of a protein (see Exhibits B and C, Invitrogen product information on Gateway vectors). The fusion of longer sequences, such as maltose binding protein (MBP) (see Exhibit D, Roche product information on MBP fusion vectors), thioredoxin (see Exhibits B and C), or glutathione transferase (GST) (see Exhibit B), is often used by a skilled artisan to allow easier production and purification of recombinant proteins. The artisan will frequently add an enzymatically cleavable linker when introducing these fusion sequences, so that they can be removed after the recombinant proteins are isolated and thus the biological functions of the proteins will remain unaltered. Enterokinase is one of the enzymes often used for this purpose (see Exhibit E, Invitrogen product information on EKMax and EK-Away). It is evident from these examples that the technology on use of epitope tags, fusion proteins, and enzyme cleavable linkers has reached a high level of sophistication.

One skilled in the art has ample guidance from any commercial supplier of suitable vectors or enzymes to make and use a fusion protein of the present invention and

will not need more detailed teaching from the application. On the other hand, the Examiner has shown no evidence supporting the assertion that the description in the application and the knowledge one skilled in the art should possess would not enable the practice of the invention as claimed. Applicants request that the enablement rejections to claims 23-27 be properly withdrawn.

B. 35 USC §102(b) or §103(a)

The Examiner rejected claims 16-30 under 35 USC §102(b) for alleged anticipation by the Soedjak reference or the Vreeland reference, or, in the alternative, under 35 USC §103(a) for alleged obviousness over the same references.

The two cited references describe the isolation and enzymatic activity of a full length, naturally-occurring vanadium bromoperoxidase found in *Fucus*, but do not disclose its amino acid sequence. The present invention discloses the amino acid sequence of the full length protein, which has 676 amino acids. Further, the present invention teaches that the C-terminal region, i.e., the 441-676 segment of SEQ ID NO:2, is sufficient for enzymatic activity. The subject matter of the pending claims after the amendment is a polypeptide with at least 90% amino acid sequence identity to the 441-676 segment of SEQ ID NO:2, which also is capable of catalyzing ODA oxidation and has ***no more than about 600 amino acids in length***. Thus, the full length vanadium bromoperoxidase that naturally occurs in Fucus, which has 676 amino acids, is not within the scope of the claims as amended. Applicants respectfully request that the rejections under 35 USC §102 be withdrawn.

The Examiner bears the initial burden of factually supporting prima facie conclusion of obviousness. To establish a prima facie case of obviousness, three criteria must be met. First, there must be some suggestion or motivation provided by prior art or the general knowledge one skilled artisan is expected to have to make the modification; second, there must be a reasonable expectation of success; third, prior art must teach or suggest all elements of the claims. MPEP §2142.

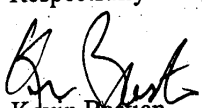
The two cited references do not disclose the amino acid sequence of the vanadium bromoperoxidase, let alone the significance of the 441-676 region of SEQ ID NO:2. The Examiner has not shown what in the two references or any prior art teaches or suggests to one of ordinary skill in the pertinent art the role of the 441-676 segment of SEQ ID NO: 2 in maintaining the catalytic activity of the enzyme. More importantly, the Examiner has pointed to nothing in the cited references that would lead one of skill to prepare a fragment of about 600 amino acids or less. There is simply no showing that the fragment was known or suggested to be sufficient to retain enzymatic activity. Since no prima facie obviousness has been established, Applicants request the withdrawal of the rejections under 35 USC §103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 576-0200.

Respectfully submitted,



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

16. (Amended) An isolated polypeptide comprising an amino acid sequence having at least 90% amino acid sequence identity to a sequence from residue 441 to residue 676 as set forth in SEQ ID NO:2, wherein the polypeptide catalyzes oxidation of o-dianisidine (ODA) when complexed with a vanadium ion, and has no more than about 600 amino acids in length.

APPENDIX B

CLAIMS SUBJECT TO EXAMINATION

16. (Amended) An isolated polypeptide comprising an amino acid sequence having at least 90% amino acid sequence identity to a sequence from residue 441 to residue 676 as set forth in SEQ ID NO:2, wherein the polypeptide catalyzes oxidation of o-dianisidine (ODA) when complexed with a vanadium ion, and has no more than about 600 amino acids in length.

17. (As filed) The isolated polypeptide of claim 16, wherein the polypeptide has at least 80% identity to a polypeptide as set forth in SEQ ID NO:2.

20. (As filed) The isolated polypeptide of claim 16, wherein the polypeptide has a molecular weight of about 58 kD.

21. (As filed) The isolated polypeptide of claim 16, wherein the polypeptide has a molecular weight of about 40 kD.

22. (As filed) The isolated polypeptide of claim 16, wherein the polypeptide is immobilized on a solid surface.

23. (As filed) The isolated polypeptide of claim 16, wherein the polypeptide further comprises a cleavable linker sequence.

24. (As filed) The isolated polypeptide of claim 23, wherein the cleavable linker sequence is an enterokinase cleavable linker sequence.

25. (As filed) The isolated polypeptide of claim 16, wherein the polypeptide further comprises an epitope tag.

26. (As filed) The isolated polypeptide of claim 25, wherein the epitope tag comprises a plurality of histidine residues.

27. (As filed) The isolated polypeptide of claim 16, wherein the polypeptide further comprises a thioredoxin sequence.

28. (As filed) A method for enzymatically halogenating a compound, the method comprising contacting the compound with an isolated polypeptide of claim 16.

29. (As filed) The method of claim 28, wherein the compound is a protein.

30. (As filed) A method for enzymatically oxidizing a compound, the method comprising contacting the compound with an isolated polypeptide of claim 16.